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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 03/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/775,341	TANAKA ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13,27-33 and 35-64* is/are pending in the application.

4a) Of the above claim(s) *9,27-33 and 35-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments/Amendments

Applicant's amendments filed 11 January 2006 to claims 1, 4, 7, 10, 32 and 35 have been entered. Claims 6, 14-26 and 34 have been cancelled. Claims 1-5, 7-13 and 27-33 and 35-64 remain pending in the current application. All arguments have been fully considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 10-13 are rejected under 35 U.S.C.103(a) as being unpatentable over Webb et al (US Patent 6,670,129), in view of Ausubel et al (Current Protocols in Molecular Biology, 1988).

Applicant's claim 1 is directed to a multiwell plate for transfecting a eukaryotic cell wherein the bottom of at least some of the wells are at least partially affixed with a composition comprising a transfection agent comprising a metal salt which is not pre-mixed with a biomolecule. Claim 2 requires the metal salt to be a calcium salt. Claim 3 requires the metal salt to be calcium chloride or calcium acetate. Claim 4 requires the composition to further comprise a matrix. Claim 5 requires the composition to be retained on the multiwell plate. Claim 7 requires the matrix complex to be proteins. Claim 8 requires the proteins to be gelatin.

Applicant's claim 10 is directed to a cell culture/transfection device for transfecting a eukaryotic cell, consisting essentially of a solid surface, wherein the solid surface is coated with calcium chloride in a gel matrix, wherein the concentration of the calcium chloride in the gel matrix is 10-40 mM. Claim 11 requires the surface to be selected from the group consisting of flasks, dishes,

tubes, multiwell plates, slides and implanted devices. Claim 12 requires the solid surface to be glass, polystyrene or epoxy resins. Claim 13 requires the solid surface to be selected from a slide and a multi-well plate.

Webb et al teach a cell transfection apparatus and a method of transfecting eukaryotic cells using the cell transfection apparatus. The cell transfection apparatus of Webb et al can comprises a multiwell plate, wherein one or more foreign biomolecules, such as DNA, are printed onto each of the wells (See Webb et al, col. 6, ln 46-col. 7, ln 20). Webb et al also teach that the biomolecules, such as DNA, can be contained in a solvent, such as gelatin (See Webb et al, col. 11, ln 53-58); therefore the cell transfection apparatus can comprise spots of DNA in gelatin. The method of performing the cell transfection is accomplished by (i) providing one of the transfection plates printed with the biomolecules (with or without gelatin); (ii) adding a transfection reagent, such as calcium phosphate, to the wells of the transfection plates so as to create a biomolecule-transfection agent complex; and then (iii) adding the desired cells and cell growth media to the wells of the microplates so the cells are exposed to the biomolecule-transfection agent complex and are successfully transfected (See col. 7, ln 21-47).

Though Webb et al describe calcium phosphate as a *transfection reagent*, it was well known to one of ordinary skill in the art at the time the invention was made that it is actually the $CaPO_4$-DNA complex, formed by mixing DNA and $CaCl_2$ in a phosphate-containing buffer, that functions as the transfection reagent in calcium phosphate mediated transfections (See, e.g., Ausubel et al, 9.1.1). Therefore, in order to form $CaPO_4$-DNA transfection reagent, one of ordinary skill in the art would add $CaCl_2$ in a phosphate-containing buffer (i.e. PBS or HEPES) to the transfection plate printed with DNA.

The cell transfection apparatus of Webb et al differs from the currently claimed product in that the transfection plate of Webb et al is initially provided with only the biomolecules (DNA), optionally in a gelatin matrix, printed on the surface, the 'transfection reagent' (determined to be

$CaCl_2$ in phosphate containing buffer) is intended to be added subsequently; alternatively, the cell transfection plate of the current invention is initially provided with only a metal salt, preferably $CaCl_2$, in a gelatin matrix, the DNA is intended to be added subsequently. However, it remains the examiner's position that it would have been well within the purview of one of ordinary skill in the art, at the time the invention was made, to initially spot either or both DNA and/or the calcium chloride in a gelatin matrix on the multiwell plate to create a cell transfection apparatus as claimed. Both the cell transfection apparatus of Webb et al and that of the current invention are intended to be used for the reverse transfection of DNA into eukaryotic cells. In order for reverse transfection to be successfully performed a transfection reagent must be formed on a substrate prior to addition of cells (See Webb et al & Ausubel et al). In calcium phosphate mediated transfection, the transfection agent is $CaPO_4$-DNA, which is formed by mixture of DNA and $CaCl_2$ in the presence of a phosphate-containing buffer (See Ausubel et al, 9.1.1); therefore, in order to prepare $CaPO_4$-DNA on the substrate both the DNA and calcium chloride must be combined in the presence of a phosphate-containing buffer. Therefore, while Webb et al teach initially starting with the biomolecules (DNA) printed in a gelatin matrix on the multiwell plate, it would have been obvious to initially print (thereby affixing) the calcium chloride in a gelatin matrix on the multiwell plate (Claims 1-8). Selection of either component to be initially present on the multiwell plate surface is considered to be prima facie obvious, as it only effects the order of mixing ingredients and selection of the order of mixing ingredients is considered to prima facie obvious. See *In re Gibson* 39 F.2d 975, 5 USPQ 230 (CCPA 1930).

One of ordinary skill in the art would have been motivated to modify the cell transfection apparatus of Webb et al so as to have calcium chloride initially printed on the surface in situations where the cell transfection apparatus is not to be used immediately. More specifically, in situations where the cell transfection apparatuses are to be prepared in bulk at one point in time, then stored for future use at a much later point in time, it would be desirable to print calcium chloride in gelatin on

the multiwell plates as opposed to DNA in gelatin, so as to prevent any spontaneous mutation, degradation, or contamination of the DNA that may result over an extended storage period. One of ordinary skill in the art will certainly recognize that DNA is more susceptible to temperature, humidity, etc than calcium chloride; therefore, in order to prevent problems that may arise during storage, and to allow for simpler storage set-ups, one of ordinary skill in the art would be motivated to create the transfection apparatuses of Webb et al with the calcium chloride initially deposited in gelatin on the multiwell plates instead of the DNA. One of ordinary skill in the art would expect success creating and using the calcium chloride printed multiwell plates because means are well known in the art for depositing small amounts of chemical (including DNA and calcium chloride) in gelatin spots to a multiwell plate (See Webb et al), and one would expect the same level of success in using the calcium chloride-gelatin printed multiwell plates because DNA in a phosphate-containing buffer could be added to the wells to form the same $CaPO_4$-DNA transfection reagent known for calcium phosphate mediated transfection.

Regarding the concentration of calcium chloride to be present in the gel matrix, it appears that this concentration is dependent on the initial quantity of calcium chloride used to form the $CaPO_4$-DNA transfection reagent. Ausubel et al teach that concentration of DNA is a result effective variable, and can vary from 10-50 ug per 10-cm dish (See Ausubel et al, pg 9.1.1); therefore, because the concentration of calcium chloride depends on the concentration of DNA used, the concentration of calcium chloride is also a result effective variable that would be routinely optimized by one of ordinary skill in the art (Claims 10 and 11).

Regarding the geometry of the substrate, though the example provided Webb et al uses a microwell plate, Webb et al also teach that the transfections can be performed on culture dishes and any other suitable substrate geometries. Therefore, though Webb et al do not specifically state flasks, tubes, slides or implanted devices, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the transfection on any solid surface, including flasks, tubes

and/or implanted devices (See Webb et al, col. 6, ln 46-63) (Claims 11 and 13). One of ordinary skill in the art would have been motivated to use any solid surface, including flasks, dishes, tubes, multi-well plates, slides, and/or implanted devices based on their personal preference and experimental design, as all are functional equivalents of one another for the present purpose. One of ordinary skill in the art would be motivated to use flasks or dishes, such as culture flasks or culture dishes, or multi-well plates because they can easily hold cell culture solution; multi-well plates would especially be useful when multiple samples of different cells are to be transfected, in order to provide separate wells for each cell type. One of ordinary skill in the art would have been motivated to use an implantable device in order to transfect cells prior to transplanting them to a patient, for example, an artificial dermis matrix that is to be used to transfect cells with growth factors to increase the survive rate of the transplanted cells. One would have expected success using any geometric surface because Webb et al teach that any solid geometric surface, suitable for the individual needs is acceptable.

Regarding the type of substrate, Webb et al teach suitable substrates can be comprised of, or coated with, glass or polystyrene (See Webb et al, col. 7, ln 66-col. 8, ln 7 & col. 8, ln 33-50) (Claim 12). Additionally, though they do not specifically list epoxy resins as a material, it would have been obvious to one of ordinary skill in the art to use epoxy resins as at least part of the solid surface (Claim 12). One of ordinary skill in the art would have been motivated to use cured epoxy resin plastics based on availability of materials, for example, if epoxy resin slides or dishes, or glass-reinforced plastics, that comprise epoxy, were readily available. One would have had a reasonable expectation of success using any glass, plastic, or epoxy resin material that is suitable grade for cell culture based on Webb et al's teachings that any suitable solid material can be used.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered. The rejection of claims 10-13 under 35 USC 112, first paragraph have been shown to have been erroneous and thus they are withdrawn. Applicants clarified the issue and pointed to specific support in the specification for the limitation regarding the concentration of the calcium chloride; the examiner regrets any inconvenience the error caused. The issues causing the rejections under 35 USC 112, second paragraph have been obviated by the current amendments. The rejections of claims 1, 2 and 4-8 over Webb et al under 35 USC 102(e) have been obviated by the current amendment.

However, all claims have now been deemed to be obvious over the teachings of Webb et al in view of Ausubel et al, for the reasons discussed above. Applicants did provide a brief argument that one of ordinary skill in the art would not be motivated to modify the teachings of Webb et al to affix a transfection reagent onto a plate without the biomolecule because Webb et al teach printing the substrate with an array of proteins or genes. Applicants state the advantage taught by Webb et al include segregation of the transfected cell from the non-transfected cells on the plates with the printed biomolecules. In response, it is noted that, for the reasons discussed above, particular to prevent problems that may arise during storage, one of ordinary skill in the art would have been motivated to modify the apparatus of Webb et al to comprise only the calcium chloride affixed to the plates, without the biomolecules. Regarding the segregation of the transfected cells from the non-transfected cells, such segregation was due to the particular geometric structure of some embodiments of Webb et al, and does not have any relevance on the presence or absence of DNA and/or calcium chloride.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER